1,3,4-Thiadiazoles and 1,3-thiazoles from one-pot reaction of bisthioureas with 2-(bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate

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Graphical Abstract

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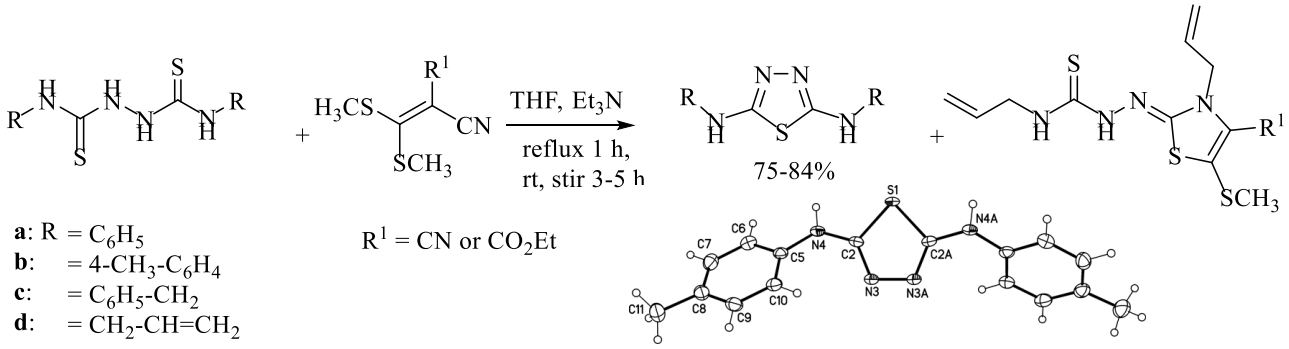

1,3,4-Thiadiazoles and 1,3-thiazoles from one-pot reaction of bisthioureas with 2-(bis(methylthio)methylene)malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate

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Abstract

Bisthioureas reacted with either 2-(bis(methylthio)methylene)malononitrile or ethyl 2-cyano-3,3-bis(methylthio)acrylate to give 1,3,4-thiadiazoles and 1,3-thiazoles. Only, the reactive allyl derivative of bisthioureas reacted with the bis(methylthio)methylene compounds to give 1,3-thiazoles. The mechanism was discussed. The structures of products were proved by MS, IR, NMR and elemental analyses and X-ray structure analysis.

Keywords: Bisthioureas, bis(methylthio)malononitrile, bis(methylthio)acrylate, 1,3,4-thiadiazoles, 1,3-thiazoles, X-ray.

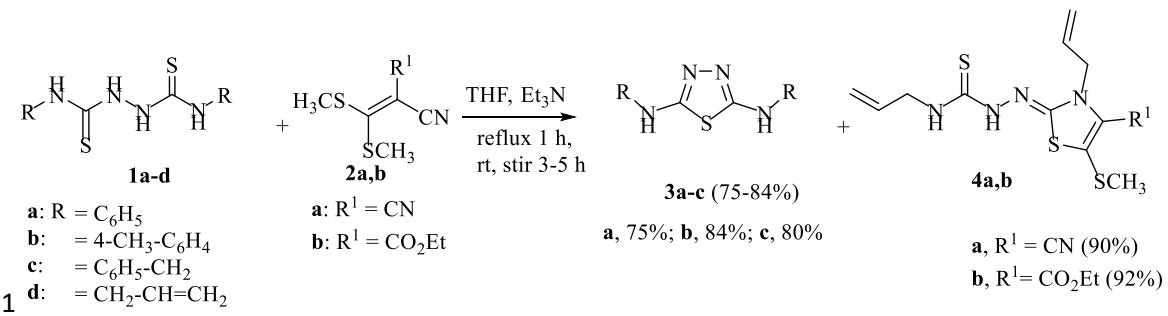
Introduction

1,3,4-Thiadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They are known to exhibit diverse biological activities such as in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities [1]. Acylated substituted 5-thio-β-*D*-glucopyranosylimino-1,3,4-thiadiazoles have been tested in *vitro* for antiviral activity against HIV-1, HIV-2 and human cytomegallo- virus (HMCV) [2]. A large number of thiadiazoles have also been patented in the agriculture field as herbicides, insecticides, fungicides, and bactericides [3]. Recently, 1,3,4-thiadiazole cores have received much attention in material science due to their interesting electronic and optical properties [4]. Various methodologies that exist in the literature [5] for their synthesis are associated with number of drawbacks that impedes their applicability in the long run. On the other hand, the thiazole nucleus is very in many biologically active compounds that makes it one of the most extensively studied heterocycles [6]. Thiazoles play a pivotal role in many drug structures. For example, Ritonavir (anti-HIV drug) [7], Dasatinib and Tiazofurin (antineoplastic agents) [8], Fanetizole, Fentiazac and Meloxicam (anti-inflammatory agents) [9], Nizatidine (antiulcer agent) [10], Ravuconazole (antifungal agent) [11], Nitazoxanide (antiparasitic agent) [12]. Inspired by these interesting previous biologically active compounds, we envisioned that treatment 2-hydrazinocarbothioyl -*N*-substituted-hydrazine-carbothioamides **1a–d** with 2-(bis(methylthio)-methylene)malononitrile (**2a**) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**) would form 1,3,4-thiadiazole and/or 1,3-thiazole derivatives.

Results and Discussion

Equimolar amounts of 2-(hydrazinocarbonothioyl)-*N*-substituted-hydrazine-carbothioamides **1a–d** and 2-(bis(methylthio)methylene)malononitrile (**2)** were stirred in tetrahydrofuran (THF) with catalytic amounts of trimethylamine (Et_3N) at refluxing temperature for 1 h and at room temperature for 1-3 h. Bis-thioureas **1a-c** provided from excellent to moderate yields of the respective diaminothiadiazoles. For the bis-arylthioureas having electron-donating substituent like **1b**, the yield of **3b** (84%) was superior to **3c** (80%, Scheme 1). In general, 1,3,4-thiazole derivatives **3a-c** were precipitated as colorless solids and as the sole products in 75–84% yields (Scheme 1). In the case of **1d** reacting with **2a** and/or **2b**, 1,3-thiazole derivatives were obtained in a different manner (Scheme 1). The mass spectrum and elemental analysis proved the molecular formula of **3a** as $C_{14}H_{12}N_4S$ (I removed the IR sentence). The phenyl protons in the ^1H NMR spectrum of **3a** appeared as two triplets at δ_H = 6.94 (J = 7.6 Hz, 2H) and 7.27 (J = 7.6 Hz, 4H) and a doublet at δ_H = 7.54 (d, J = 7.6 Hz, 4H). The NH protons were absorbed as broad singlet at δ_H = 9.38. The ^{13}C NMR spectrum indicated the ring of 1,3,4-thiadiazole ring structure, by revealing the C=N carbon signal at δ_C= 156.3.(I remove the previous sentence). All spectroscopic and analytical data are in a good agreement with the structure of (the full name was omitted) **3a** [13,14]. Similarly, compound **1b** (the full name was omitted) reacted with **2** to produce (the full name was omitted) **3b** [13]. The structure proof of **3b** was unambiguously supported by X-ray structure analysis (Figure 1). In the same manner, 1,3,4-thiadaizole-2,5-diamine derivative **3c** (the name was shortened) [14]. was obtained in 80% yield from the reaction of **1c** with **2** (Scheme 1).

The newly prepared 3-thioxo-1,2,4-triazolidine-1-carbothioamide **4a** (the name was shortened) was obtained as pale red crystals in 90% yield (Scheme 1).



Scheme 1. Reactions of bisthioureas **1a-d** with π-deficient compounds **2a,b**

The results of combustion analyses and spectroscopic data suggested the molecular weight of the products results from the sum of the two reactants **1d** with **2a** accompanied by loss of a HCN molecule (see the experimental section). The IR spectrum showed the amino and nitrile groups at ν_{max} = 3230 and 2210 cm^{-1}. The thiocarbonyl group absorbed in the IR spectra at ν_{max} =1225 cm^{-1}. The ^{1}H NMR spectrum revealed the SMe protons as a singlet at $\delta_H = 2.60$. The two allyl-CH_2N protons appeared as two broad singlets in different regions at $\delta_H = 4.28$ and 3.90 (see the experimental section). Allyl-CH= and allyl-CH_2= protons resonated as two multiplets and appeared at $\delta_H = 5.80–5.72$ (2H) and 5.20-5.14 (4H). The ^{13}C NMR spectrum of **4a** supported the allylic structure of **4a** and exhibited peaks at δ_C =133.0, 130.8 (allyl-CH=), 118.2, 116.1 (allyl–CH_2=), and 44.0, 42.6 (CH_2). Moreover, the exo-azomethine carbon (thiazole C-2) appeared in the ^{13}C NMR of **4a** at $\delta_C = 154.0$ (see the experimental section). Whilst, the distinctive thioamide (C=S) and the nitrile carbons appeared at $\delta_C = 180.2$ and 115.0, respectively. The same trend was obtained during the reaction of **1d** with ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**). (the sentence here was wrong and omitted). Compound (the full name was omitted) **4b** was obtained during reaction of **1d** with **2b** (Scheme 1). The structure of **4b** was proved by IR, NMR and elemental analysis and was supported by mass spectroscopy and elemental analysis that gave its molecular formula as $C_{14}H_{20}N_4O_2S_3$. IR showed the NH

stretching at ν_{max} = 3330-3240, whereas the aliphatic and carbonyl groups appeared at ν_{max} = 2960-2870 and 1700 cm^{-1}, respectively. Strong vibrational coupling was also noted due to the nitrogen containing thiocarbonyl derivative appeared at ν_{max} = 1390 cm^{-1}. ^{1}H NMR spectrum of **4b** revealed the ester group as a triplet at δ_H = 1.22 (J = 7.2 Hz) and quartet at δ_H = 4.00. The SMe protons resonated as a singlet in the ^{1}H NMR spectrum centered at δ_H = 2.65, whereas the two allyl-NCH_2 protons appeared as two broad singlets in different regions at δ_H = 4.20 and 3.90 (see the experimental section). Two multiplets were recognized in the ^{1}H NMR spectrum of **4b** indicated the allylic asymmetric structure (allyl-CH= and allyl-CH_2=) of **4b**, appeared at δ_H = 5.86–5.80 (2H) and 5.19-5.15 (4H). The ^{13}C NMR spectrum of **4b** indicated the allylic carbons at δ_C = 116.5, 118.0 (allyl NCH_2=), 133.2, 130.6 (allyl-CH=), and 44.8, 42.4 (allyl-CH_2-N). The exo-azomethine carbon of thiazole C-2 appeared at δ_C = 152.0 (see the experimental section). Mechanistically, the reaction between **1a-c** and **2a** or **2b** can be described as due to nucleophilic attack of the sulfur lone pair of **1** at the C-2 carbon of **2** to form salt **5** (Scheme 2). Thereafter, further nucleophilic attack of the other sulfur lone pair at the positively charged thiocarbonyl would cause cyclization to give intermediate **6**. The cyclization is followed by hydrogen transfer followed by neutralization to form **3a-c** and **7**. Ultimately, elimination of H_2S from **7** would reproduce **2** (Scheme 2). It might therefore be concluded that compound **2** initiates internal cyclization process of **1a-c**. The same trend occurs between **1d** and **2a,b** to form salt **5** (Scheme 3). Instead of the aforementioned second step in Scheme 2, neutralization occurred *via* proton transfer to form intermediate **8** (Scheme 3). Finally cyclization occurs with the nitrogen lone pair accompanied by elimination of the HCN molecule to form **4a** or **4b** (Scheme 3)

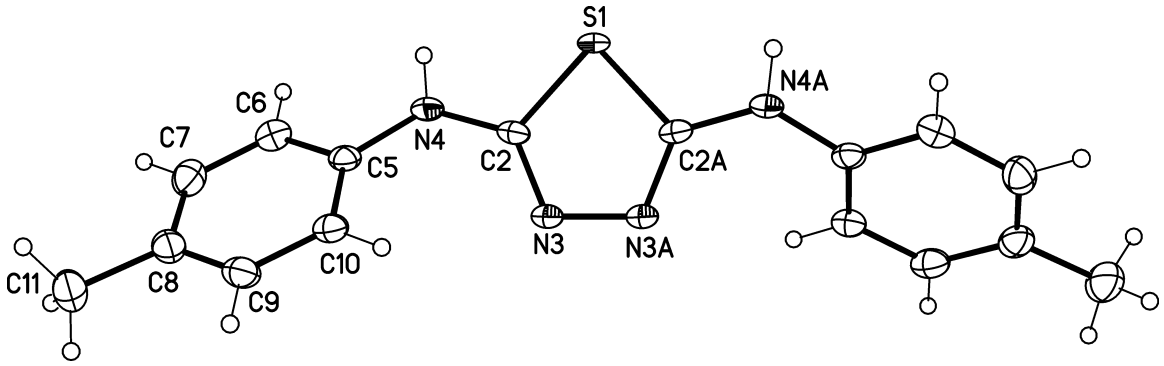
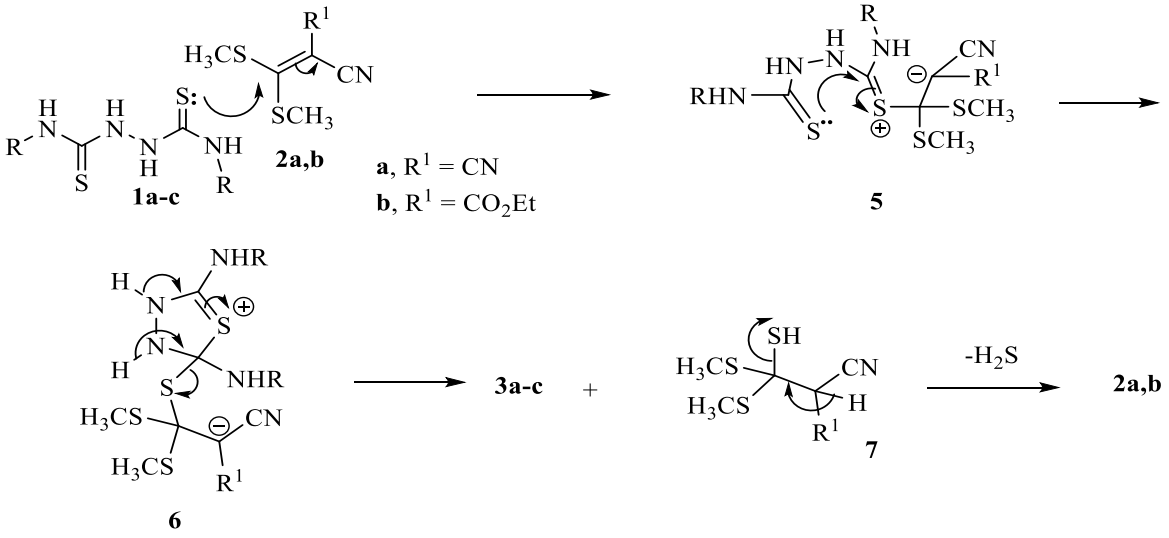
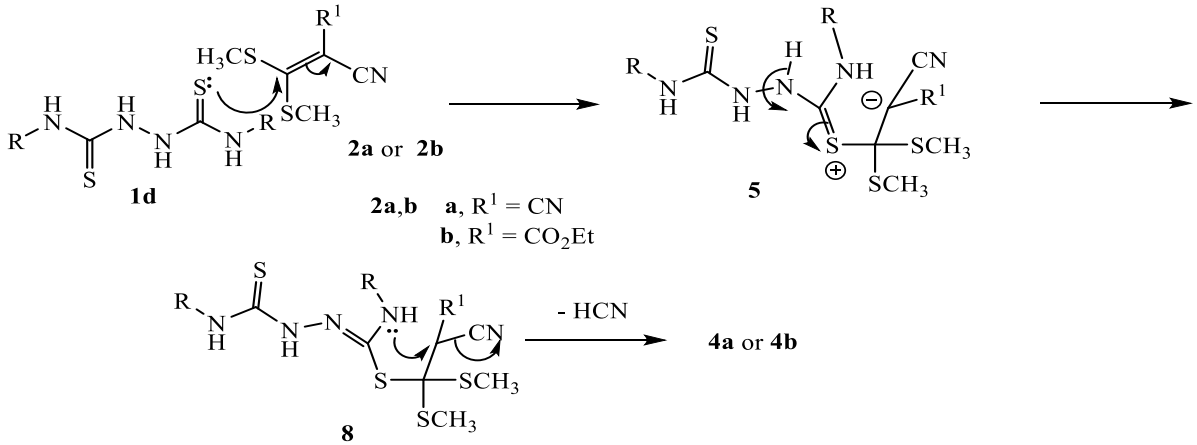


Figure 1. Molecular structure analysis of *N*,*N*'-bis(4'-methylphenyl)-1,3,4-thiadiazole-2,5-diamine (**3b**) with crystallographic C_2-symmetry (displacementparameters are drawn at 50% probability level)



Scheme 2. Plausible mechanism of internal cyclization **1a-c** during its reaction with **2a,b**
(The scheme was declared)



Scheme 3. Plausible mechanism describing reaction between **1d** and **2a,b**
(the scheme was declared)

Conclusion

Although there are many reports of the synthesis of thiadiazoles, few reports are available for the synthesis of symmetrical 2,5-disubstituted amino-1,3,4-thiadiazoles in the literature. Therefore our method is a valuable addition to the literature for the synthesis of this class of compound in good yields without requiring the aforesaid hazardous acidic conditions.

Experimental

Melting points are uncorrected. The IR spectra were recorded as KBr disks on a Shimadzu-408 infrared spectrophotometer, Faculty of Science, Minia University. TLC analysis was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. The NMR spectra were measured using a Bruker AV-400 spectrometer at Institute of Organic Chemistry, Karlsruhe, Germany. Chemical shifts were expressed as δ (ppm) with tetramethylsilane (TMS) as internal reference. The samples were dissolved in DMSO-d_6, s = singlet, d = doublet, dd = doublet of doublet and t = triplet. Mass spectra were recorded on Varian MAT 312 instrument in EI mode (70 eV), Centre of National Research, Dokki, Cairo, Egypt. Elemental analyses were carried out using Varian Elementary device in the National Research Center, Giza, Egypt, or by the Microanalytical Unit at Cairo University, Cairo, Egypt.

Crystal Structure Determination of 3b

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Ka radiation (l = 1.54178 Å. Direct Methods (SHELXS-97) [G. M. Sheldrick, *Acta Crystallogr*. 2008, **A64**, 112-122] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [G. M. Sheldrick, *Acta Crystallogr*. 2015, **C71**, 3-8]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). A semi-empirical absorption corrections was applied.

3b: colourless crystals, $C_{16}H_{16}N_4S$, M_r = 296.39, crystal size 0.36 × 0.18 × 0.09 mm, monoclinic, space group *P*bca (No. 60), a = 6.6154(3) Å, b = 8.5679(3) Å, c = 25.561(10) Å, V = 1448.80(10) Å^3, Z = 4, ρ = 1.359 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.963 mm^{-1}, F(000) = 624, $2\theta_{max}$ = 144.4°, 7112 reflections, of which 1435 were independent (R_{int} = 0.026), 100 parameters, 1 restraint, R_1 = 0.031 (for 1316 I > 2σ(I)), wR_2 = 0.086 (all data), S = 1.03, largest diff. peak / hole = 0.227 / -0.273 e Å^{-3}. CCDC 1494906 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Starting materials

1,6-Disubstituted 2,5-dithioureas were parepared according to published procedures as were *N,N'*-diphenylhydrazine-1,2-dicarbothioamide (**1a**) and *N,N'*-bis(benzyl)hydrazine-1,2-dicarbothioamide (**1c**) [14] and *N,N'*-bis(4'-methylphenyl)hydrazine-1,2-dicarbothioamide (**1b**) [14] and *N,N'*-diallylhydrazine-1,2-dicarbothioamide (**1d**) [4,14]. 2-(bis(methylthio)-methylene)malononitrile (**2a**) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2b**) were bought from Fluka.

General Procedure

Reaction of bisthioureas 1a-d with compounds 2a or 2b

A mixture of a dithiouears (**1a-c**, 1 mmol), an activated nitrile **2a** or **2b** (1 mmol), and a few drops of triethylamine in THF (30 mL) gently refluxed for 1 h; the reaction was followed by TLC analysis. After cooling at room temperature, the the preceiptates of **3a-c** were collected by suction filtration, washed with THF, and dried at room temperature. Compounds **3a-c** were identified by comparing their mp,s, IR and NMR spectra and their analytical data.

N,N'-Diphenyl-1,3,4-thiadiazole-2,5-diamine (**3a**), colourless crystals (DMF), 0.20 g, (75%), m.p. 239-240 °C (lit. [13,14] 239-240 °C).

N,N'-Bis(4'-methylphenyl)-1,3,4-thiadiazole-2,5-diamine (**3b**), colourless crystals (DMF), 0.25 g (85%), m.p. 137-138 °C (lit. [13,14] 240-243 °C).

N,N'-Bis(benzyl)-1,3,4-thiadiazole-2,5-diamine (**3c**). colourless crystals (MeOH), 0.24 (80%), m. p. 138-140 °C (lit. [14] 137-139 °C).

Z-*N*-Allyl-2-(3-allyl-4-cyano-5-(methylthio)thiazol-2(3*H*)ylidene)hydrazine-1-carbothioamide (**4a**). Pale yellow crystals ($CHCl_3$/MeOH), 0.28 g (90%), m.p. 166-168 °C. IR (ν_{max}): = 2980-2860 (Aliph-CH), 3230 (NH), 2210 (CN), 1225 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 10.20 (s, 1H, NH), 9.40 (s,1H, NH), 5.80–5.72 (m, 2H, allyl=CH), 5.20-5.14 (m, 4H, allyl-CH_2=), 4.28 (bs, 2H, allyl-NCH_2), 3.90 (bs, 2H, allyl-NCH_2), 2.60 (s, 3H, SCH_3). ^{13}C NMR (DMSO-d_6): δ_C = 180.2 (C=S), 154.0 (C=N), 133.0, (allyl-CH=), 131.6 (C-4), 130.8 (allyl-CH=), 129.2 (C-5), 118.2, 116.1 (allyl-NCH_2), 115.0 (CN), 44.0, 42.6 (CH_2), 15.4 (SCH_3). MS (70 eV, %): *m/z* = 325 (M^+, 100), 310 (22), 278 (18), 252 (24), 137 (24). Calcd for $C_{12}H_{15}N_5S_3$ (325.47): C, 44.28; H, 4.65; N, 21.52. Found: C, 44.10; H, 4.55; N, 21.65.

Ethyl (Z)-3-allyl-2-(3-allylcarbamothioyl)hydrazono-5-(methylthio)-2,3-dihydrothiazole-4-carboxylate (**4b**). Pale yellow crystals (MeOH), 0.34 g (92%), m.p. 198-200 °C. IR (ν_{max}): = 2960-2870 (Aliph-CH), 3240 (NH), 1700 (CO-ester), 1390 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 10.20 (s, 1H, NH), 9.40 (s,1H, NH), 5.86–5.80 (m, 2H, allyl=CH), 5.19-5.15 (m, 4H, allyl-CH_2=), 4.20 (bs, 2H, allyl-NCH_2), 4.00 (q, 2H, CH_2-ester), 3.90 (bs, 2H, allyl-NCH_2), 2.65 (s, 3H, SCH_3), 1.22 (t, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6): δ_C = 180.4 (C=S), 165.4 (CO-ester), 152.0 (C=N), 133.2, 130.6 (NCH=), 130.2 (C-4), 129.2 (C-5), 118.0, 116.5 (allyl=CH_2), 50.0 (CH_2-ester), 44.8, 42.4 (allyl-NCH_2), 15.4 (SCH_3), 12.4 (CH_3-ester). MS (70 eV, %): *m/z* = 325

(M^+, 100), 310 (22), 278 (18), 252 (24), 137 (24). Calcd for $C_{14}H_{20}N_4O_2S_3$ (372.52): C, 45.14; H, 5.41; N, 15.04. Found: C, 45.30; H, 5.55; N, 15.20.

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